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(71) Applicant: S.A.ATTA APPLICATIONS ET TRANSFERTS DE TECHNOLOGIES AVANCEES [FR/FR]; 173, avenue Saint-Lambert, F-06100 Nice (FR).

(72) Inventors: KRAFFT, Marie-Pierre; 34, rue Vernier, F-06100 Nice (FR). RIESS, Jean, G.; Les Giaines, F-06950 Falicon (FR).

(74) Agent: STUART, Ian; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).

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(54) Title: VISCOELASTIC COMPOSITIONS OF FLUORINATED ORGANIC COMPOUNDS

(57) Abstract

Compositions for topical application in gel form comprising a fluorocarbon or perfluorocarbon compound or mixtures thereof at a concentration of at least about 75 % v/v, a minor quantity of a surface active agent and an aqueous phase. The compositions provide a storage-stable high concentration fluorocarbon gel that is prepared without the use of thickeners or additional stabilizing agents. The gels are useful in formulations for pharmaceutical, cosmetic purposes and for other products as well.

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VISCOELASTIC COMPOSITIONS OF FLUORINATED ORGANIC COMPOUNDS

Technical Field

The present invention relates to viscoelastic compositions or gels which may have uses in cosmetics, biology, therapeutics and elsewhere, eg as protective creams and lubricating agents. It relates particularly to viscoelastic compositions that have high concentrations of highly fluorinated or perfluorinated compounds.

Fluorocarbons have numerous biomedical applications because of their high chemical and biological inertness and their capacity to dissolve a considerable amount of gases, particularly oxygen, carbon dioxide and air per unit volume. Indeed, at 37°C under a pure oxygen atmosphere, a fluorocarbon can dissolve about 50% of its volume of oxygen.

Background Art

Compositions of fluorocarbons can also be used for the treatment of wounds, for example burns, as described in U.S. Patent 4,366,169. According to this disclosure, the wound is put in contact with a liquid fluorocarbon directly, or indirectly through a dressing, for example a sponge, gauze, foam, dispersion or gel into which the fluorocarbon has been incorporated. However, the '169 patent does not disclose a high concentration fluorocarbon formulation or a procedure for preparing a fluorocarbon-rich gel.

High concentration fluorocarbon formulations can increase the gas-transfer capacity of preparations for topical application, improving their therapeutic effects and protecting the tissues coated therewith. Highly viscous preparations of this type can be easily applied to the wounded tissues.

Fluorocarbons have been used in the form of emulsions or water-rich gels. Known gel formulations contain low concentrations of fluorocarbons and require stabilizing or thickening agents to maintain a

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desirable consistency. Thus, U.S. Patent No. 5,073,378 describes compositions for the treatment of burns, obtained from solutions of collagen, containing a growth-factor derived from platelets, and a fluorocarbon phase whose perfluorocarbon content is low. U.S. Patent No. 4,917,930 and EP-A-0158996 describe compositions in the form of fluorocarbon emulsions comprising no more than 50% fluorocarbon by weight, or about 25% fluorocarbon by volume. These compositions are obtained by preparing an initial dispersion comprising a fluorocarbon and a surfactant complexed with the fluorocarbon, and then concentrating the fluorocarbon phase of the dispersion, for example by centrifugation, separating the fluorocarbon-rich phase, and redispersing this phase in an aqueous medium optionally containing a surfactant. Although this procedure makes it possible to limit the quantity of surfactant used, does not provide formulations having fluorocarbon concentrations greater than 50% by weight. The emulsions obtained by this process are intended to be injectable.

U.S. Patent No. 4,569,784 describes a stable gel of fluorocarbon also comprising no more than 50% by volume of fluorocarbon, which requires considerable quantities of surfactant for stabilization. This gel is prepared by a similar complex procedure of concentrating an emulsion by centrifugation, and requires high-pressure apparatus or the use of ultrasound.

FR-A-2 630 347 describes fluorocarbon gels comprising, by contrast with those described in the above patents, a high proportion of water, about 60 to 98% by weight.

WO-A-93/09762 describes the use of fluorocarbon suspensions or emulsions for intravascular applications, containing at most 90 g/100 ml (about 50% v/v).

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WO-A-90/15807 describes the use of phosphorus-containing fluorinated surfactants in fluorocarbon emulsions and other compositions containing at most 70% in volume of fluorocarbons.

Obraztsov (poster contribution to the fifth ISBS, San Diego California, USA, March 1993) describes an emulsion prepared from a mixture of fluorocarbons containing perfluorodecalin (80% w/v, 40% v/v), emulsified using a polyoxyethylene/polyoxypropylene copolymer (Proxanol 268) and gelified by 1,2-propyleneglycol. Preliminary studies have shown that this emulsion has a beneficial effect on the speed of cicatrization of burns and surgical wounds (activation of keratinocytes) and should be more efficacious than the biostimulating medicaments traditionally used (methyluracyl and solkoseryl). But the fluorocarbon content of these preparations does not exceed 50% by volume and the gelification is obtained by the use of a non-surfactant diol.

Disclosure of the invention

In one aspect the invention provides a viscoelastic gel composition having an oily phase and an aqueous phase, wherein:

(a) the oily phase comprises at least one fluoro-compound, the or each said fluoro-compound being a linear, branched and/or cyclic hydrocarbon (which may be saturated or unsaturated, and which may have one or more heteroatoms interposed in its carbon chain) whereof at least 30% of the hydrogen atoms are replaced by fluorine (and optionally one or more hydrogen atoms are replaced by Br and/or Cl and/or I);

(b) said at least one fluoro-compound constitutes 75 to 99.7% (v/v) of the composition;

(c) said aqueous phase represents 0.3 to 25% (v/v) of the composition; and

(d) said composition includes at least one fluorinated surfactant, optionally together with one or more non-fluorinated surfactants, the total

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surfactant content being 0.1 to 10% (w/v) of the composition.

Embodiments of the present invention may provide compositions comprising highly fluorinated or perfluorinated organic compounds formulated as gels having highly viscoelastic properties. They also provide procedures to gelify fluorocarbon. Certain of these compositions are perfectly transparent. Embodiments may be useful in many applications, but particularly in medicine, pharmacy, cosmetics and in biological applications.

Preferred compositions, having a higher fluorocarbon concentration than previously known compositions of the same type, are advantageously used as topical applications. Preferred compositions are stable, easily sterilized by heat, and are easy to prepare without requiring thickening by addition of a gelifying agent.

They may be in the form of a viscoelastic gel, stable and permeable to gases.

Definitions

In the description of the invention; unless the context requires otherwise,

gel designates a semi-solid, apparently homogenous substance which can have the consistency of gelatin.

highly fluorinated or perfluorinated compound designates linear, branched or cyclic hydrocarbons, saturated or unsaturated, or derivatives of these, which are partially or totally fluorinated.

perfluorinated designates a totally fluorinated compound.

partially fluorinated signifies that at least 30% of the hydrogen atoms of the hydrocarbon or of its derivative have been replaced by fluorine atoms.

derivatives are fluorinated compounds, for example, wherein heteroatoms, such as O or S, are inserted into the carbon chain and/or wherein the

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hydrogen atoms of the hydrocarbon are substituted by Br, Cl or I as well as fluorine.

Modes for carrying out the Invention

The fluorinated organic compound can be chosen, for example, among the fluorocarbons and perfluorinated compounds such as linear, branched, cyclic or polycyclic perfluoroalkanes, perfluoroethers, perfluoropolyethers, perfluoroamines, freons, mixed fluorinated/hydrogenated compounds, perfluoroalkyl bromides or chlorides and mixed derivatives, which can be partially fluorinated and partially hydrogenated. Suitable compounds are perfluorodecalin, 1,2-bis(F-alkyl)ethenes (1,2-bis(F-butyl)ethene, 1-F-isopropyl,2-F-hexylethene and 1,2-bis(F-hexyl)ethene), perfluoromethyldecalin, perfluorodimethyldecalin, perfluoromethyl-, and dimethyladamantane, perfluoromethyl-dimethyl- and trimethylbicyclo (3,3,1) nonane and homologs, perfluoroperhydrophenanthrene, ethers of formulae: $(CF_3)_2CFO(CF_2CF_2)_2OCF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_3OCF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)_2F$, $(CF_3)_2CFO(CF_2CF_2)_3F$, $F[CF(CF_3)CF_2O]_2CHFCF_3$, $[CF_3CF_2CF_2(CF_2)u]_2O$ with u= 1, 3 or 5, amines $N(C_3F_7)_3$, $N(C_4F_9)_3$, $N(C_5F_{11})_3$, perfluoro-N-methylperhydroquinoline and perfluoro-N-methylperhydroisoquinoline, perfluoroalkyl hydrides such as $C_6F_{13}H$, $C_8F_{17}H$, $C_8F_{16}H_2$ and the halogenated derivatives $C_6F_{13}Br$, $C_8F_{17}Br$ (perflubron), $C_6F_{13}CBr_2CH_2Br$, 1-bromo 4-perfluoroisopropyl cyclohexane, $C_8F_{16}Br_2$, $CF_3O(CF_2CF_2O)_uCF_2CH_2OH$ with u=2 or 3. Examples of mixed fluorinated/hydrogenated compounds are $C_6F_{13}C_{10}H_{21}$, $C_6F_{13}CH=CHC_6H_{13}$, $C_8F_{17}CH=CHC_8H_{17}$. Examples of fluorinated polyethers are $CF_3[(OCF_2CF_2)_p(OCF_2)_qCF_3$, where p/q = 0.6 to 0.7. These compounds can be used alone or in mixtures.

According to a preferred embodiment, the highly fluorinated or perfluorinated compound used comprises from 2 to 20 carbon atoms, preferably from 6 to 20 carbon atoms and more preferably from 8 to 20 carbon atoms.

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Preferably, according to the invention, the highly fluorinated or perfluorinated compound of the composition has a high boiling point, for example above 140°C, so that its evaporation is slow and it is well adapted to use in the form of a salve or ointment. For applications in which a faster evaporation of a fluorocarbon from a gel is desirable, a fluorocarbon having a lower boiling point can be used.

Examples of high boiling point fluorocarbon compounds are:

perfluoroperhydrophenanthrene (bp 215°C)
perfluoroperhydrofluoranthene (bp 240°C)
perfluorotributylamine (bp: 178°C)
bis(perfluorohexyl)1,2-ethene (bp 195°C)
perfluorofluorene (bp 194°C); and
APF-215™, APF-240™, APF-260™ (Air Products, USA) (bp 215, 216 and 260°C respectively).

Other highly fluorinated compounds useful in the invention are

perfluorodiisopropyldecalin
perfluoro-n-butyldecalin
perfluorodixylylmethane
perfluorodixylylethane
perfluorooctyl bromide
perfluoropolyethers, for example, the fomblins™ of Ausimont of various molecular weights, for examples MW 2500 and 3300,
$C_{10}F_{21}H$
$C_2F_3Cl_3$

The surfactants used in the invention can be perfluoroalkylated surfactants alone or in mixtures with one or more hydrogenated surfactants. By "perluoroalkylated" is meant that the surfactant contains a perfluoroalkyl group. Preferably it also contains a (non-fluorinated) alkyl group. The surfactants can be non-ionic, anionic, cationic or zwitterionic or mixtures thereof.

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For applications in the biomedical or cosmetic field, surfactants known by those skilled in the art to be the most biocompatible are used. Accordingly, perfluoroalkylated surfactants are preferred, as they are much more efficacious and less toxic than their hydrocarbon analogs, particularly because they have low hemolytic activity (J.G. Riess et al, Adv. Mat., 3:249-251 (1991).

For example, compounds of formula I detailed hereafter tolerated at doses up to 1.25g/kg after intravenous injection in mice of a dispersion of these compounds in physiological saline. Compounds of WO-A-91/914689, telomeric amphiphilic surfactants, used in this invention are tolerated up to 4g/kg after intravenous injection in mice of a dispersion of these compounds in physiological saline.

Examples of suitable perfluoroalkylated surfactants are the amine oxides described in U.S.Patent 3,828,085, in particular those having the formula $R_F(CH_2)_nCONH-R^1-N(O)R^2R^3$ ("formula I") wherein

R_F is a perfluoroalkyl group of from 4 to 12 carbon atoms;

R^1 is an alkyl group of from 1 to 6 carbon atoms;

R^2 and R^3, which can be identical or different, are selected from the group consisting of alkyl groups of from 1 to 6 carbon atoms or alkyl groups of from 2 to 16 carbon atoms having a hydroxyl terminus; or fluorinated phosphorus derivatives such as those described in WO-A-90/5807, in particular fluorinated derivatives of phosphocholine, or fluorinated telomeric surfactants such as those described in WO-A-91/914689.

The quantities of surfactants used in the invention are low (0.1 to 10% w/v) and are chosen in relation with the quantity of aqueous phase used such

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that the weight ratio of surfactant/aqueous phase is from 1/10 to 1/1, preferably from 1/5 to 1/3.

The compositions of the invention can be prepared by low-energy mechanical homogenization techniques, in particular, which are far easier to operate than those such as sonication or high-energy homogenization formerly used for the preparation of fluorocarbon gels.

Thus, the invention provides a procedure for the preparation of the composition of fluorinated organic compounds described above, comprising the steps of:

(a) dispersing at least one suitable surfactant in the aqueous phase by mechanical stirring;

(b) progressively adding to the dispersion of step (a), under stirring, the required quantity of oily phase fluorocarbon to form a gel of fluorinated compound(s); and optionally

(c) degassing the gel of step (b).

The degassing can be done for example, by centrifugation at room temperature.

Using the procedure described, a concentrated gel is obtained without the necessity of an intermediate step of preparing an emulsion which is then concentrated by centrifugation by expensive techniques or thickened as described in the prior art. The preparation of gels is far simpler than that described in U.S. Patent No. 4,569,784 for preparing fluorocarbon emulsions because the techniques of low-energy dispersion are sufficient to form the gels, whereas for the preparation of classical emulsions, mechanical high-pressure homogenizers of the Manton-Gaulin type, or microfluidizer or ultrasound must be used.

When the composition of the invention is to be used for biomedical applications, the gel can be sterilized; this can be done, for example, by heating in a static autoclave under standard procedures.

When the composition comprises additives, these can be added to the aqueous phase, the oily phase or

to both phases. The additives can be mineral salts, buffers, oncotic and osmotic agents, nutritive agents, active principles, medicinal substances, filters of particular rays, or other ingredients that improve the stability, efficacy and biological tolerance of the compositions.

The compositions of fluorinated compounds of the invention present characteristics very different from those of known emulsions and fluorocarbon gels. The gels compositions of the invention are often in the form of transparent gels, as compared to the milky emulsions.

Also, the concentration of perfluorinated compound of the present gel compositions is far higher (75 to 99.7% v/v) than the maximum concentration of up to about 70% (v/v) in known compositions, and the ratio of surfactant to the highly fluorinated or perfluorinated compounds, necessary for the preparation of the composition, is far lower than that used in known compositions.

The quantity of water which can be incorporated in the gel is variable and can be adapted to the intended application. Indeed, some compositions may contain only 0.3% of water, but others may contain up to 25% (v/v) of water. In the latter case, greater quantities of surfactant are generally used, because for a given concentration of surfactant, the viscosity of the gel is decreased as the quantity of water increases. For a given amount of water, the viscosity can be increased by increasing the proportion of surfactant. A surfactant to aqueous phase ratio of 1/5 generally provides a satisfactory viscosity for many uses.

Moreover, the preparation of the gels of the invention does not require the addition of a gelifying agent, and these gels can be sterilized by heat under standard conditions, and stored for several months at room temperature, without apparent degradation.

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The compositions of highly fluorinated or perfluorinated compounds of the invention can find numerous applications, in particular in cosmetics and pharmacy as well as in light radiation protective or other barrier creams. Their use in ophthalmology is also contemplated. They can also be used in cutaneous applications for the healing of wounds, burns, and bruises, and for the reduction of hypertrophic scars. Indeed, highly fluorinated or perfluorinated compounds, being both hydrophobic and lipophobic, have the property, when spread over the skin (the wound), of isolating the skin and forming a barrier to all forms of contamination and to dust, while remaining permeable to gas and particularly to oxygen. An efficacious protection can also be obtained with thin films of gel of highly fluorinated or perfluorinated compounds. Moreover, these gels can also contain medicaments, for example growth-factors, antibiotics, nutritive elements or other beneficial substances, for example hydrating agents, which will thus be delivered at the appropriate site. The gels of highly fluorinated or perfluorinated compounds have in addition lubricating properties, improving the slipperiness and reducing friction.

The compositions of the invention can also be used to realize more complex formulations permitting the simultaneous delivery of hydrophilic and lipophilic drugs.

The compositions of the invention can also be incorporated into a dressing to be applied on the skin. The term dressing here includes any medical material destined to maintain the gel in contact with the skin and perhaps to apply pressure, for topical treatments in the biomedical or cosmetic field. The gels can be incorporated into or deposited on various supports for other applications.

The compositions of the invention can also be used in any application related to the particular properties of the compositions and in particular to

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their highly viscoelastic character, their transparency, their surface active character, their chemical inertness, their permeability to oxygen, and if necessary to those of other additives present in the composition.

Other characteristics and advantages of the invention will be more clearly seen on reading the following examples, which are illustrative, not limitative.

Some embodiments of the present invention will now be described in detail using the following examples; however, the methods described therein are broadly applicable, and are not to be understood as limited thereby in any way whatsoever. In the following examples, all temperatures are set forth uncorrected in degrees Celsius.

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EXAMPLES

Examples 1 to 7 : Preparation of perfluorodiisopropyldecalin gel (APF-240)™.

In these examples, pentadecafluoroheptylamidopropyl -dimethylamine oxide (F7AO) according to formula I, is used as a surfactant. The appearance of the gels obtained in Examples 1-7 was unchanged after 1 year of storage at room temperature.

EXAMPLE 1

In this example, a high proportion of fluorocarbon (99% v/v) was used. The surfactant F7AO (0.045g, 0.2% w/v) was dispersed by mechanical stirring in water for injectable preparations (0.225g, 1% v/v) at a temperature of 20 to 30°C. A quantity of 22.28ml of perfluorodiisopropyldecalin (44.55g, 99% v/v) was then added under a flow of nitrogen at 20-30°C, while stirring with a mixer, and the stirring was continued for 10 min.

The gel thus obtained was degassed by centrifugation at 1000 rpm for 15 min at room temperature, then conditioned in 5 ml flasks and sterilized in a static autoclave at 121°C for 15 min under a pressure of 10^5Pa (10^5N/m^2). The viscosity of the gel at 25°C was determined with a Bohlin CS rheometer (3 ml cells).

The results obtained are shown in Table I.

EXAMPLE 2

The procedure described in Example 1 was followed to prepare a fluorocarbon gel composition, using 0.112g of surfactant F7AO, 0.562g of injectable water and 21.94ml (43.88g) of perfluorodiisopropyldecalin. A gel containing 97.5% v/v of fluorocarbon, 2.5% v/v of water and 0.5% w/v of surfactant was thus obtained. The composition and viscosity of the gel are shown in Table I.

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EXAMPLE 3

The procedure described in Example 1 was followed starting with 0.225g of surfactant F7AO, 1.125g of injectable water and 21.37ml (42.75g) of perfluorodiisopropyldecalin. The composition and viscosity of the gel are shown in Table I.

EXAMPLE 4

The procedure described in Example 1 was followed to prepare a gel using 0.187g of surfactant F7AO, 0.560g of injectable water and 21.94ml (43.88g) of perfluorodiisopropyldecalin.

The composition and viscosity of the gel are shown in Table I.

EXAMPLE 5

The procedure described in Example 1 was followed starting with 0.750g (3.33% w/v) of F7AO, 2.25g (10% v/v) of injectable water and 20.25ml (40.50g, 90% v/v) of perfluorodiisopropyldecalin.

The composition and viscosity of the gel are shown in Table I.

EXAMPLE 6

The procedure described in Example 1 was followed starting with 0.9g (4% w/v) of F7AO, 4.5g (20% w/v) of injectable water and 18.00ml (20% v/v) of perfluorodiisopropyldecalin. The composition and viscosity of the gel are shown in Table I.

EXAMPLE 7

The procedure described in Example 1 was followed starting with 0.023 g of F7AO (0.1% w/v), 0.12 g of injectable water (0,1% v/v), and 22.3 ml (99.5% v/v) of perfluorodiisopropyldecalin.

EXAMPLE 8

Preparation of a gel of perfluoroperhydrophenanthrene and perfluoro n-butyldecalin (APF-215)™.

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A gel of perfluoroperhydrophenanthrene and perfluoro n-butyldecalin at a combined concentration of 99% in volume was prepared following the procedure described in Example 1 but using the following components:

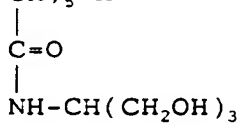
Perfluoroperhydrophenanthrene and perfluoro n-butyldecalin: 22.27ml (44.55g)
injectable water: 0.225g (1% v/v)
surfactant F7AO: 0.045g (0.2 % w/v).

The composition and viscosity of the gel are shown in Table I. No modification in the appearance of the gel was seen after one year of storage at room temperature.

EXAMPLE 9

A low viscosity gel of perfluoroperhydrophenanthrene* and perfluoro n-butyldecalin at a combined concentration of 90% in volume was prepared following the procedure described in Example 1 but using the following components:

perfluoroperhydrophenanthrene and n-butyldecalin: 9 ml
injectable water : 1 ml (1% w/v)
$C_9F_{17}(CH_2)$-S-$(CH_2$-CH$)_5$-H : 0.2 g (2% w/v)



EXAMPLE 10

Preparation of a gel of bis(perfluorohexyl)1,2-ethene.

The procedure described in Example 1 was followed to prepare a concentrated gel (99% in volume) of bis(perfluorohexyl)1,2-ethene, using the following components:

bis(F-hexyl)1,2-ethene: 22.27ml;
injectable water: 0.225g (1% v/v); and
surfactant F7AO: 0.045g (0.2% w/v)

The composition and viscosity of the gel are shown in Table I. No change in the appearance of the gel

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obtained in was seen after one year of storage at room temperature.

EXAMPLES 11 to 13:

Preparation of gels of various fluorocarbons concentrated to 95% in volume, using F7A0 as surfactant.

In these examples, various fluorocarbons, and the same proportions of fluorocarbon (95% v/v), water (5% v/v) and surfactant (1% w/v) are used.

EXAMPLE 11

The procedure described in Example 1 was followed to prepare a fluorocarbon gel, but using as fluorocarbon APF-260™, i.e. a mixture of perfluorodixylylmethane and perfluorodixylylethane.

The quantities of fluorocarbon, water and fluorinated surfactant were as follows:

fluorocarbon APF-260™: 21.37ml (42.75g)
injectable water: 1.125g, and
surfactant F7A0: 0.225g.

The composition and viscosity of the gel are shown in Table I.

EXAMPLE 12

The procedure of Example 1 was used. In addition the mixed fluorocarbon/hydrocarbon compound $C_6F_{13}C_{10}H_{21}$ was dispersed with F7A0 in water.

Fluorocarbon APF-260	:	94% v/v
$C_6F_{13}C_{10}H_2$	:	0.74% v/v
F7A0	:	0.82% w/v
Injectable Water	:	5.26% w/v

The gel is stable for at least one year.

EXAMPLE 13

The procedure described in Example 1 was followed to prepare a gel of perfluorodecalin, using the following components:

perfluorodecalin: 21.37ml, 41.46g,
injectable water: 1.125g, and
surfactant F7A0: 0.225g.

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The composition and viscosity of the gel are shown in Table I.

EXAMPLE 14

A gel of perfluorooctyl bromide was prepared, following the same operation procedure as in Example 1, but using the following components:

perfluorooctyl bromide: 21.37ml, 41.03g,
injectable water: 1.125g, and
surfactant F7AO: 0.225g.

The composition and viscosity of the gel are shown in Table I.

EXAMPLE 15

Preparation of a gel of perfluorooctyl bromide using as surfactant
2-(heptadecafluorooctyl)ethylphosphocholine (F8C2PC)

The procedure described in Example 1 was followed to prepare this perfluorooctyl bromide gel, using the following components:

perfluorooctyl bromide: 21.37ml, 41.03g (95% v/v)
injectable water: 1.125g (5% v/v), and
surfactant F8C2PC: 0.225g (1% w/v).

The composition and viscosity of the gel are shown in Table I.

EXAMPLES 16 to 19:

Preparation of gels of perfluoropolyethers of different molecular weights concentrated to 99 and 95% by volume, using F7AO as surfactant.

EXAMPLE 16

Perfluoropolyether (Ausimont, (I-20121 Milan, Italy) Product, MW(aver) = 2500 g) (99% v/v)

The procedure described in Example 1 is followed to prepare a gel of perfluoropolyether concentrated to 99% by volume, using the following components:

perfluoropolyether : 22.27 ml
injectable water: 0.225 g (1% v/v)
surfactant F7AO: 0.045 g (0.2% w/v)

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The appearance of the gel obtained was unchanged after 3 months storage at room temperature.

EXAMPLE 17

Perfluoropolyether (Ausimont Product, MW_{av} = 2500g (95% v/v)

The procedure described in Example 1 is followed to prepare a gel of Perfluoropolyether concentrated to 95% by volume, using the following components:

perfluoropolyether : 21.37 ml
injectable water: 1.125 g (5% v/v)
surfactant F7AO: 0.225 g (1% w/v)

The appearance of the gel remained unchanged after 3 months storage at room temperature.

EXAMPLE 18

Perfluoropolyether (Ausimont Product, MW = 3300 g) (99% v/v)

The procedure described in Example 1 is followed, to prepare a gel of perfluoropolyether concentrated to 99% by volume, using the following components:

perfluoropolyether : 22.27 ml
injectable water: 0.225 g (1% v/v)
surfactant F7AO: 0.045 g (0.2% w/v)

The appearance of the gel obtained was unchanged after 3 months storage at room temperature.

EXAMPLE 19

Perfluoropolyether (Ausimont) MW_{av} = 3300 g) (95% v/v)

The procedure described in Example 1 was followed to prepare a gel of perfluoropolyether concentrated to 95% by volume, using the following components:

perfluoropolyether: 21.37 ml
injectable water: 1.125 g (5% v/v)
surfactant F7AO: 0.225 g (1% w/v)

The appearance of the gel obtained was unchanged after 3 months storage at room temperature.

EXAMPLE 20

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Preparation of a gel of $C_2F_3Cl_3$ at 99% by volume using F7A0 as surfactant.

The procedure described in Example 1 was followed to prepare a gel of $C_2F_3Cl_3$ concentrated at 99% by volume, using the following components:

$C_2F_3Cl_3$	:	6.33 ml	(99% v/v)
Injectable Water	:	0.1 ml	(1% v/v)
Surfactant F7A0	:	0.02 g	(0.2% w/v)

EXAMPLES 21-22: Tolerance of the concentrated fluorocarbon gel

EXAMPLE 21

The gel formulation of Example 7 was tested for adverse effects on normal and scarified skin of 3 rabbits, as follows.

A quantity of 0.5 ml of the gel was applied to the skin of the animals for 4 hours with a semi-obstructed dressing. The dressing was then removed and the reactions were noted after 1 hour and every day for 14 days.

No irritation was observed on the normal and the scarified skin.

EXAMPLE 22

The procedure of Example 21 was followed using the gel of Example 7 (fluorocarbon 95% v/v, F7A0, 1% w/v, water 5% v/v).

No irritation was observed after 14 days.

TABLE I

Examples	Fluorocarbon (% v/v)	Water (% v/v)	Surfactants (% w/v)	Ratio of Surfactant /Water	Viscosity (Pa.s) at $0.1s^{-1}$
1	perfluorodiiso-propyldecalin (99)	1	F7AO 0.2	1/5	140.2
2	perfluorodiiso-propyldecalin (97,5)	2.5	F7AO 0.5	1/5	83.2
3	perfluorodiiso-propyldecalin (95)	5	F7AO 1	1/5	56.5
4	perfluorodiiso-propyldecalin (97,5)	2.5	F7AO 0.83	1/3	203.5
5	perfluorodiiso-propyldecalin (90)	10	F7AO 3.33	1/3	122.7
6	perfluorodiiso-propyldecalin (80)	20	F7AO 4	1/5	57.9
7	perfluorodiisopropyl decalin (99.5)	0.5	0.1	1/5	—
8	perfluoroperhydro phenanthrene and perfluoro n-butyldecalin (99)	1	F7AO 0.2	1/5	64.07
10	Bis(perfluorohexyl) 1,2-ethene (99)	1	F7AO 0.2	1/5	--
11	Perfluorodixylyl methane and perfluorodixylyl ethane (95)	5	F7AO 1	1/5	--
13	Perfluorodecalin (95)	5	F7AO 1	1/5	--
14	Perfluorooctyl bromide (95)	5	F7AO 1	1/5	--
15	Perfluorooctyl bromide (95)	5	F8C2PC 1	1/5	

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The described embodiments are to be considered in all respects only as illustrative and not restrictive, and the scope of the invention is therefore indicated by the appended claims rather than by the foregoing description. All modifications which come within the meaning and range of the lawful equivalency of the claims are to be embraced within their scope.

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CLAIMS

1. A viscoelastic gel composition having an oily phase and an aqueous phase, wherein:

(a) the oily phase comprises at least one fluoro-compound, the or each said fluoro-compound being a linear, branched and/or cyclic hydrocarbon (which may be saturated or unsaturated, and which may have one or more heteroatoms interposed in its carbon chain) whereof at least 30% of the hydrogen atoms are replaced by fluorine (and optionally one or more hydrogen atoms are replaced by Br and/or Cl and/or I);

(b) said at least one fluoro-compound constitutes 75 to 99.7% (v/v) of the composition;

(c) said aqueous phase represents 0.3 to 25% (v/v) of the composition; and

(d) said composition includes at least one fluorinated surfactant, optionally together with one or more non-fluorinated surfactants, the total surfactant content being 0.1 to 10% (w/v) of the composition.

2. A composition according to claim 1 wherein said at least one fluoro-compound comprises a perfluorinated compound.

3. A composition according to claim 1 or 2 wherein the at least one fluoro-compound represents at least 80% v/v of the composition.

4. A composition according to Claim 1 or 2,

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wherein the at least one fluoro-compound represents at least 90% v/v of the composition.

5. A composition according to any preceding claim wherein the at least one fluoro-compound has from 2 to 20 carbon atoms.

6. A composition according to any preceding Claim wherein the fluoro-compound is one or more selected from: perfluoroperhydrofluoranthrene; perfluorooctyl bromide; one or more perfluoropolyethers; perfluorodecalin; perfluoroperhydrophenanthrene; bis(perfluoro-hexyl)-1,2-ethene; a mixture of perfluorodixylylmethane and perfluorodixylylethane optionally together with $C_2 F_{13} C_{10} H_{21}$; perfluoroisopropyldecalin; a mixture of perfluoroperhydrophenanthrene and perfluoro n-butyl decalin; and $C_2 F_3 Cl_3$.

7. A composition according to any preceding claim wherein the at least one fluoro-compound has a boiling point above 140°C.

8. A composition according to any of claims 1 to 7, wherein the surfactant is an amine oxide corresponding to the formula $R_F(CH_2)_n$-CONH-$R^1N(O)R^2R^3$

wherein

R^F is a perfluoroalkyl group having from 4 to 12 carbon atoms;

R^1 is an alkyl group having from 1 to 6 carbon atoms;

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R^2 and R^3, which can be identical or different, are selected from alkyl groups having from 1 to 6 carbon atoms and alkyl groups having from 2 to 16 carbon atoms and having terminal hydroxyl groups; and n = 0 to 12.

9. A composition according to any preceding claim, wherein the surfactant is or includes pentadecafluoroheptylamidopropyldimethylamine.

10. A composition according to any of claims 1-9 wherein at least one surfactant is a fluorinated substituted phosphocholine.

11. A composition according to Claim 10, wherein the surfactant is or includes 2-(heptadecafluorooctyl)ethylphosphocholine

12. A composition according to any preceding claim wherein the surfactant is or includes at least one fluorinated telomer.

13. A composition according to claim 12 wherein said telomer comprises

$$C_8F_{17}CH_2\text{-}S\text{-}(CH_2\text{-}\underset{\displaystyle CO\,|\,NHCH(CH_2OH)_3}{CH})_5\text{-}H.$$

14. A composition according to any preceding claim wherein the weight ratio of surfactant/aqueous phase is from 1/10 to 1/1.

15. A composition according to Claim 14 wherein the weight ratio of surfactant/aqueous phase is from 1/5 to 1/3.

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16. A composition according to any preceding claim further comprising at least one additional substance present in either the aqueous or the oily phase or in each of the two phases, wherein the additive substance is selected from nutritive agents, medicinal substances, mineral salts, oncotic agents, osmotic agents, buffers and radiation filters.

17. A method for preparing a composition of one or more organic fluorinated compounds in the form of a viscoelastic gel, comprising the steps of:

(a) dispersing at least one surfactant in an aqueous phase by mechanical stirring, and

(b) adding to this dispersion a quantity of oily phase, comprising at least one flouro compound as defined in claim 1 or in an amount sufficient to form a gel.

18. The method of claim 17 as applied to the preparation of a composition according to any of claims 1-16.

19. A method according to Claim 17 or 18 further comprising heat sterilization of the gel of step (b).

20. A medical device comprising a composition according to any of claims 1 to 1.

21. A method for topically treating the skin of a mammal in need thereof comprising applying a device according to Claim 20 to the skin.

22. A pharmaceutical or cosmetic or barrier product comprising a fluorocarbon composition

according to any of claims 1 to 16.

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 94/03276

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 158 996 (ADAMANTECH INC) 23 October 1985 see claims 1,3,6,8 see page 8, line 32 - page 9, line 14 see page 9, line 25 - page 10, line 29 see page 14, line 5 - line 8 see page 15, line 9 - line 12 see page 18, line 27 - line 31 see page 21, line 10 - line 21 see examples 1,2 ---	1-22
A	WO,A,93 09762 (LONG, DAVID ET AL.) 27 May 1993 see page 12, line 29 - page 13, line 30 see page 18, line 5 - line 12 see page 19, line 7 - line 26 --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 February 1995	22.02.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Ventura Amat, A

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Int. onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,90 15807 (APPLICATIONS ET TRANSFERTS DE TECHNOLOGIES AVANCEES) 27 December 1990 see the whole document	1-22
A	WO,A,93 09787 (HEMAGEN/PFC) 27 May 1993 see the whole document	1-22

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